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Review article

Achieving asthma control with ICS/LABA: A review of strategies for asthma management and prevention

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ABSTRACT

Maintenance treatment with an inhaled corticosteroid (ICS) and a long-acting β_2-agonist (LABA) is recommended for patients whose asthma is not controlled with a low-to-moderate dose of ICS alone; a separate reliever medication is used on an as-needed basis. The Gaining Optimal Asthma ControL (GOAL) study demonstrated that salmeterol/fluticasone maintenance treatment can improve asthma control and reduce future risk compared with fluticasone alone, although the dose escalation design of this study meant that most patients treated with salmeterol/fluticasone were receiving the highest dose of ICS at the end of the study. Similarly, budesonide/formoterol maintenance therapy improved asthma control and reduced future risk compared with budesonide alone in the Formoterol and Corticosteroids Establishing Therapy (FACET) study. An alternative approach to asthma management is to use an ICS/LABA for both maintenance and reliever therapy. A large body of clinical evidence has shown that the use of budesonide/formoterol in this way improves both current control and reduces future risk compared with ICS/LABA plus as-needed short-acting β_2-agonist (SABA), even when patients receive lower maintenance doses of ICS as part of the maintenance and reliever therapy regimen. In addition, one study has shown that beclometasone/formoterol maintenance and reliever therapy reduces exacerbations more effectively than beclometasone/formoterol plus as-needed SABA. The use of ICS/LABA as both maintenance and reliever therapy ensures that an increase in reliever use in response to worsening symptoms is automatically matched by an increase in ICS.

Contents

Abbreviations: ACQ, Asthma Control Questionnaire; bd, twice-daily; CI, confidence interval; FACET, Formoterol and Corticosteroids Establishing Therapy; GINA, Global Initiative for Asthma; GOAL, Gaining Optimal Asthma ControL; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

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1. Introduction

Asthma is a major public health problem worldwide, which, when uncontrolled, can severely limit the patient's daily life [1]. The primary aim of treatment is to achieve and maintain overall asthma control by reducing the severity of current symptoms and minimising future risk [1,2]. Current control is characterised by the frequency of symptoms, use of reliever medication, lung function and physical activity limitation. Future risk includes longer-term factors such as the frequency of exacerbations, decline in lung function over time and adverse effects of treatment [1,2].

Maintenance treatment with an ICS and a LABA, either separately or as a fixed-dose formulation, is recommended for patients whose asthma is not adequately controlled when treated with a low-to-moderate dose of ICS alone; a separate reliever inhaler is used on an as-needed basis [1]. Many different ICS/LABA fixed-dose combinations are available for use in patients with asthma. For example, budesonide/formoterol and salmeterol/fluticasone propionate (from herein referred to as fluticasone) have been available for many years and their efficacy in patients with asthma has been demonstrated in several large-scale randomised trials [3,4]. More recently, beclometasone/formoterol, fluticasone/formoterol and vilanterol/fluticasone furoate have been approved for use in adult patients with asthma [5–9]. Mometasone/formoterol is also available in the USA [10].

An alternative approach to the management of asthma is to use budesonide/formoterol or beclometasone/formoterol as both maintenance and reliever therapy, providing patients with a simplified treatment regimen that requires only a single inhaler. By employing this treatment strategy, patients receive ICS in addition to a fast-acting bronchodilator whenever they require reliever medication, meaning that inflammation can be targeted when symptoms increase [11]. This approach has shown utility in the management of asthma [12–19], and is recommended by GINA and approved for use in Europe and a number of other countries around the world [1].

In this article, the role of ICS/LABA in the management of asthma will be reviewed, considering both current control and future risk. We will summarise results from the landmark GOAL and FACET studies, which demonstrated the advantages of adding a LABA to an ICS by comparing salmeterol/fluticasone or budesonide/formoterol with ICS alone [3,4]. We will then explain how data from the budesonide/formoterol and beclometasone/formoterol maintenance and reliever therapy studies [12–17,19], in particular, expand upon the findings of both GOAL and FACET.

2. Achieving current control and reducing future risk: the ICS/LABA approach

In patients whose asthma is not well controlled with a low dose of ICS, there are two possible strategies that can be used to improve control: increasing the dose of ICS or adding a LABA [1]. However, concern has been expressed that the addition of a LABA to a low dose of ICS may enhance current control but mask inflammation, therefore increasing future risk [20,21].

In the FACET study, patients who had stable asthma after a run-in period were randomised to receive budesonide (at a low or high dose) in combination with either formoterol or placebo (Table 1) [3]. Patients were eligible for inclusion if they had been diagnosed with asthma for at least six months and had been treated with an ICS for at least three months, although patients receiving high doses of ICS at baseline were excluded. The addition of formoterol to budesonide enhanced current control compared with an increased dose of budesonide. Indeed, the addition of formoterol to budesonide was associated with a significantly higher number of episode-free days and greater improvements in day and night-time symptom scores compared with the same dose of budesonide alone ($p = 0.001$). While the mean number of episode-free days was significantly increased with the addition of formoterol 12 μg to twice-daily budesonide 100 μg (metered dose), there was no significant increase with twice-daily budesonide 400 μg alone (Fig. 1A). In contrast, although the addition of formoterol to a low dose of budesonide decreased future risk by reducing the rate of severe exacerbations by 26%, a greater reduction was achieved

Table 1
Overview of study design and patient numbers in the FACET [3] and GOAL [4] studies.

Parameter	FACET [3]	GOAL [4]
Patients, n	852	3039[a]/2890[b]
Run-in period		
Treatment received	BUD 800 μg	Usual dose (if any) of ICS
Duration, weeks	4	4
Study duration, months	12	12
Study interventions[c]	1. BUD 100 μg + placebo 2. BUD 100 μg + FORM 12 μg 3. BUD 400 μg + placebo 4. BUD 400 μg + FORM 12 μg	1. FLU (100, 250 or 500 μg) 2. SAL/FLU (50/100, 50/250 or 50/500 μg)
Dosing frequency	Twice daily	Twice daily

All BUD and FORM doses are shown as metered dose.
BUD, budesonide; FACET, Formoterol and Corticosteroids Establishing Therapy; FLU, fluticasone; FORM, formoterol; GOAL, Gaining Optimal Asthma ControL; ICS, inhaled corticosteroid; SAL, salmeterol.
[a] Completed phase 1: dose escalation phase in which treatment was stepped up every 12 weeks until total asthma control was achieved or highest dose of study drug reached (SAL/FLU 50/500 μg or FLU 500 μg bd).
[b] Completed phase 2: remained on dose at which they achieved total asthma control or the maximum dose of study medication until the end of the 12-month double-blind treatment period.
[c] Patients were randomised to one of the treatment arms.

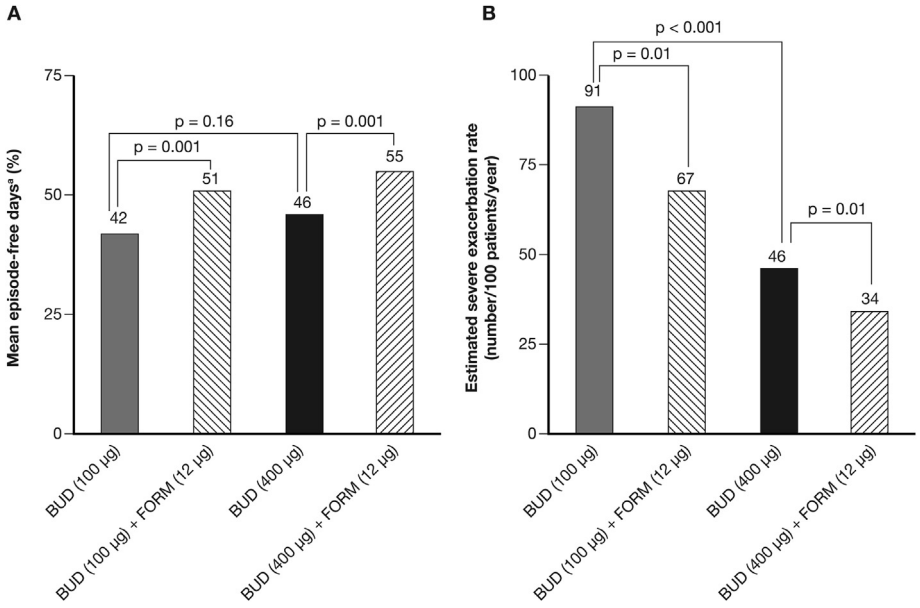

Fig. 1. Mean episode-free days (A) and number of severe exacerbations (B) among patients treated with twice-daily budesonide or budesonide/formoterol in FACET [3]. [a] Days with no symptoms or rescue medication use and PEF >80% of baseline value. BUD, budesonide; FACET, Formoterol and Corticosteroids Establishing Therapy; FORM, formoterol; PEF, peak expiratory flow.

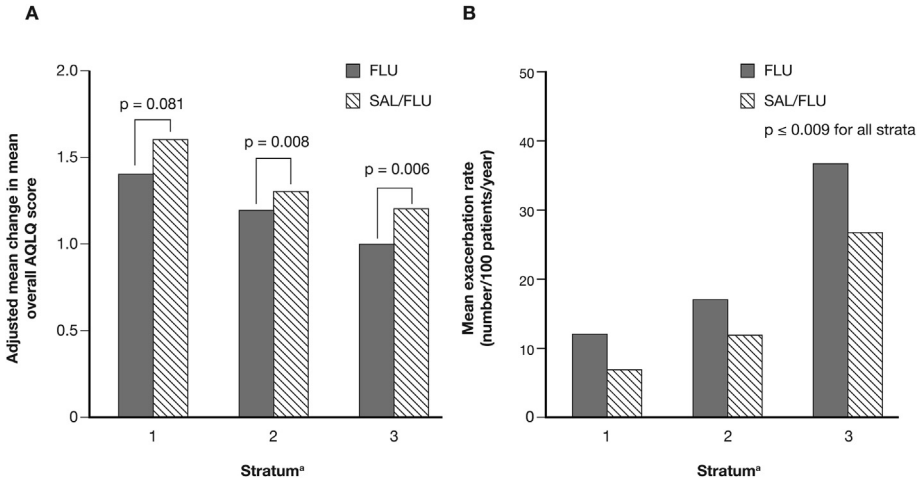

Fig. 2. Adjusted mean change from baseline in mean overall AQLQ score (A) and mean exacerbation rate (B) among patients treated with twice-daily fluticasone or salmeterol/fluticasone in GOAL, stratified by pre-study ICS dose [4]. [a] Strata were based on ICS dose in the 6 months before screening; stratum 1, no ICS; stratum 2, ≤500 µg of beclometasone dipropionate daily or equivalent; stratum 3, >500 µg to ≤1000 µg of beclometasone dipropionate daily or equivalent. AQLQ, Asthma Quality of Life Questionnaire; FLU, fluticasone; GOAL, Gaining Optimal Asthma ControL; ICS, inhaled corticosteroid; SAL, salmeterol.

when increasing the metered twice-daily dose of budesonide from 100 µg to 400 µg (Fig. 1B) [3].

In the GOAL study, patients were randomised to salmeterol/fluticasone or fluticasone alone if they did not achieve at least two well-controlled weeks in a four-week run-in period (Table 1) [4]. Patients were stratified by their pre-study ICS dose (stratum 1, no ICS; stratum 2, ≤500 µg of beclometasone dipropionate daily or equivalent; stratum 3, >500 µg to ≤1000 µg of beclometasone dipropionate daily or equivalent). The study was split into two phases; a dose-escalation phase followed by a phase during which patients remained on their maximum dose of treatment. The addition of salmeterol to fluticasone improved health status and significantly reduced the exacerbation rate compared with fluticasone alone (Fig. 2A and B), suggesting that salmeterol contributes to improved current control and reduced future risk. However, the design of this study meant that is was not possible to determine whether the addition of salmeterol to fluticasone was more beneficial than increasing the dose of fluticasone alone.

3. Achieving current control and reducing future risk: limitations of aiming for total control

In the GOAL study, significantly more patients treated with salmeterol/fluticasone achieved total asthma control, defined as achievement of 7 out of 8 weeks with no exacerbations, no nighttime awakening, morning peak expiratory flow ≥80% predicted every day, no symptoms, no need for rescue β_2-agonist use, no emergency room visits and no treatment-related adverse events requiring a change in asthma therapy, than those receiving fluticasone alone [4]. However, total asthma control was still only

achieved by a minority of patients who were treated with salmeterol/fluticasone. Interestingly, many of these patients achieved total asthma control at the lowest dose of ICS (100 μg bd for strata 1 and 2; 250 μg bd for stratum 3), despite the majority of patients (68%) who were treated with salmeterol/fluticasone receiving the highest dose of fluticasone at the end of the study. The results of this study therefore bring into question the benefits of increasing the maintenance dose of ICS until total control is achieved, especially as the lack of a down-titration plan in this study meant that many patients received the highest dose of ICS for prolonged periods of time without achieving total asthma control [4]. Interestingly, the results of the FACET study do suggest that a higher dose of ICS may be advantageous for patients receiving ICS/LABA maintenance treatment, as an increase in dose of ICS was associated with a reduction in future exacerbation risk [3]. However, 34% of patients still experienced severe exacerbations despite being treated with the highest dose of budesonide/formoterol (400/12 μg bd; metered dose) in this study (Fig. 1B).

The benefit of increasing the maintenance dose of ICS has been investigated in other studies [22,23]. In one study, 61 patients with poorly controlled asthma were treated with budesonide at a delivered dose of either 2560 μg or 1280 μg daily, in order to assess whether asthma outcomes were improved when ICS treatment was started at the higher dose [22]. Down-titration of the ICS dose was allowed after 16 weeks in patients whose asthma was controlled. A starting dose of 1280 μg was found to be sufficient to achieve optimal asthma control, and there was no significant improvement in airway hyper-responsiveness for patients treated with budesonide 2560 μg compared with the lower dose ($p = 0.7$). However, airway hyper-responsiveness did reach normal levels significantly more rapidly when patients were treated with budesonide 2560 μg ($p = 0.03$) [22]. In another study, patients with well-controlled asthma were randomised to receive twice-daily salmeterol/fluticasone at a dose of either 50/250 μg or 50/500 μg [23]. Improvements in airway hyper-responsiveness were again more rapid in patients receiving the higher dose of ICS, although this difference was not statistically significant. However, over the last eight weeks of randomised treatment, the lower dose of ICS was sufficient to maintain well-controlled asthma and there were no significant differences between the two groups. Interestingly, other studies have shown that an increased dose of ICS may be necessary to reduce airway inflammation in patients with asthma [24–26]. In one study, a significantly smaller reduction in sputum eosinophils was observed for patients who were treated with budesonide plus formoterol compared with a four-fold higher dose of budesonide alone ($p < 0.001$) [24]. In another study, treatment with budesonide/formoterol was associated with a greater increase in sputum eosinophils compared with a four-fold higher dose of budesonide (3.41% vs. 1.74%), although this was not found to be statistically significant [25].

4. Achieving current control and reducing future risk: ICS/LABA maintenance and reliever therapy

An alternative strategy to asthma management is to use ICS/LABA as both maintenance and reliever therapy, and because of its rapid onset of action, formoterol is suitable for use in this way in combination with budesonide or beclometasone [27]. Indeed, budesonide/formoterol maintenance and reliever therapy has been investigated in several clinical trials and real-world studies [12–18,28–31], and has a similar efficacy and safety profile to salbutamol over a period of 3 h in the management of acute bronchoconstriction in patients with asthma; its bronchodilator activity is apparent one minute after treatment [32,33]. There is less evidence for the use of beclometasone/formoterol for maintenance and relief, but this regimen was found to be more effective at reducing asthma exacerbations than beclometasone/formoterol plus as-needed salbutamol in one trial [19]. Consequently, the use of budesonide/formoterol or beclometasone/formoterol maintenance and reliever therapy is recommended in global asthma treatment guidelines as an alternative to treatment with an ICS/LABA plus a separate reliever medication [1].

4.1. ICS/LABA maintenance and reliever therapy: beyond FACET and GOAL

The use of budesonide/formoterol as maintenance and reliever therapy has been compared with all alternative standard treatment strategies in patients with moderate-to-severe asthma [12–17]. In particular, the STAY [14], COMPASS [16] and AHEAD [17] studies built on GOAL and FACET by comparing budesonide/formoterol maintenance and reliever therapy with two different doses of budesonide/formoterol plus SABA, budesonide plus SABA and salmeterol/fluticasone plus SABA. In the STAY study, 2760 patients received budesonide/formoterol (80/4.5 μg bd) plus SABA, budesonide (320 μg bd) plus SABA or budesonide/formoterol maintenance and reliever therapy (80/4.5 μg bd) for 12 months to establish whether the latter approach could improve current control and reduce future risk [14]. Treatment with budesonide/formoterol for maintenance and relief improved current asthma control compared with a higher dose of budesonide plus SABA or the same dose of budesonide/formoterol plus SABA, as demonstrated by a significant reduction in daytime and night-time reliever use and night-time symptom scores (all $p < 0.001$). Additionally, morning peak expiratory flow was significantly improved versus the other treatment regimens (Fig. 3A; $p < 0.001$), and the rate of severe exacerbations was significantly reduced compared with both control arms (Fig. 4A; $p < 0.001$).

The effect of budesonide/formoterol maintenance and reliever therapy (160/4.5 μg bd), a higher dose of budesonide/formoterol (320/9 μg bd) plus SABA or salmeterol/fluticasone (50/250 μg bd) plus SABA on overall asthma control was assessed in the COMPASS study, which included 3335 patients [16]. Asthma Control Questionnaire scores over the duration of the study were similar for all three treatment groups (Fig. 3B), indicating that use of budesonide/formoterol for maintenance and relief was as effective as the higher dose of budesonide/formoterol plus SABA or salmeterol/fluticasone plus SABA at improving current asthma control. This regimen also resulted in the lowest rate of severe exacerbations (Fig. 4B). Similar results were observed in the AHEAD trial, in which 2309 patients were treated with salmeterol/fluticasone (50/500 μg bd) plus SABA or budesonide/formoterol maintenance and reliever therapy (320/9 μg bd) [17]. In this study, current control was improved to a similar extent in both groups, as indicated by comparable changes in ACQ-5 scores from baseline (Fig. 3C). Severe exacerbations occurred less frequently among patients treated with budesonide/formoterol for maintenance and relief compared with salmeterol/fluticasone plus SABA (Fig. 4C; $p < 0.05$).

The STAY, COMPASS and AHEAD studies have demonstrated how the use of budesonide/formoterol as maintenance and reliever therapy provides current control and minimises future risk without utilising the high maintenance doses of ICS that are sometimes required with other treatment regimens [3,4,14,16,17]. Indeed, patients using budesonide/formoterol as maintenance and reliever therapy in the COMPASS study had a lower mean ICS load than those receiving a higher dose of budesonide/formoterol plus SABA, despite using the ICS/LABA combination as reliever medication [16]. However, concern has been expressed that budesonide/formoterol reliever medication could increase the risk of adverse events due to both short-term and cumulative exposure to treatment.

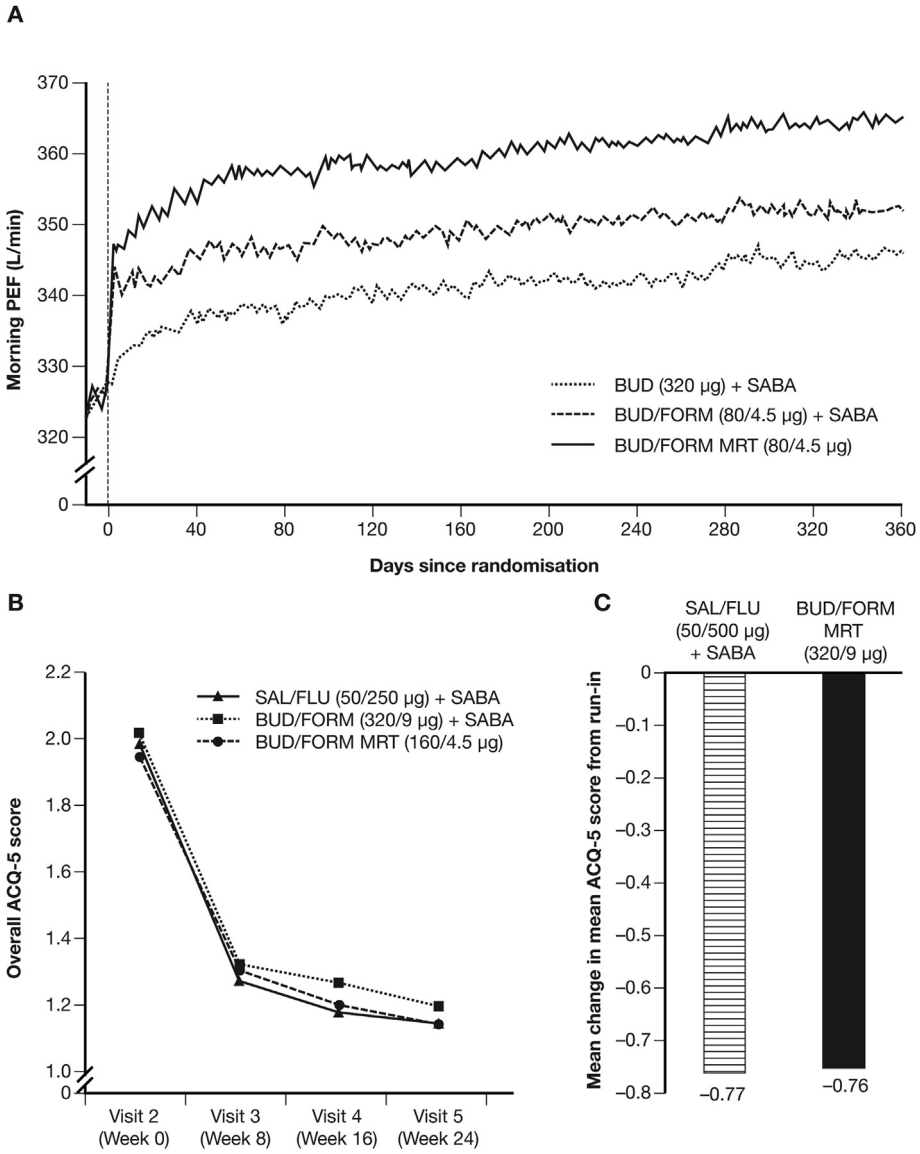

Fig. 3. Current asthma control with twice-daily treatment in STAY (A) [14], COMPASS (B) [16] and AHEAD (C) [17]. ACQ-5, Asthma Control Questionnaire (5-item version); BUD, budesonide; FLU, fluticasone; FORM, formoterol; MRT, maintenance and reliever therapy; PEF, peak expiratory flow; SABA, short-acting β_2-agonist; SAL, salmeterol.

Consequently, a randomised controlled trial was conducted by Patel et al. to assess the risk–benefit profile of the maintenance and reliever therapy approach [28]. In this study, patients received twice-daily maintenance therapy with budesonide/formoterol (400/12 µg bd metered dose, equivalent to 320/9 µg bd delivered dose) plus either budesonide/formoterol or SABA as reliever medication; electronic monitoring was used to assess patterns of medication use. As could be expected with such a trial design, patients receiving budesonide/formoterol for both maintenance and relief had a greater exposure to ICS than those using a SABA, and these patients had significantly fewer days in which they received zero actuations of budesonide/formoterol ($p = 0.022$). As budesonide/formoterol maintenance and reliever therapy reduced severe exacerbations compared with budesonide/formoterol plus SABA, patients treated with this regimen had a lower oral corticosteroid exposure meaning that the overall corticosteroid burden was similar between the two groups. The frequency of adverse events was also similar between the two groups. Budesonide/formoterol maintenance and reliever therapy therefore has a favourable risk–benefit profile in adults at risk of severe asthma exacerbations.

In contrast to budesonide/formoterol, the use of beclometasone/formoterol maintenance and reliever therapy has only been investigated in one study, a 48-week, multicentre, double-blind, randomised, controlled trial that included 1714 patients with asthma that was not fully controlled [19]. In this study, the time to first exacerbation, defined as admission to hospital or visit to an emergency department, or use of systemic steroids for ≥3 consecutive days, was significantly increased with beclometasone/formoterol maintenance and reliever therapy compared with beclometasone/formoterol plus as-needed salbutamol (209 days and 134 days, respectively), corresponding to a 36% reduction in risk (HR 0.64 [95% CI 0.49 to 0.82]; $p = 0.0005$); both treatments were well tolerated. Consequently, this study demonstrated that the use of beclometasone/formoterol for maintenance and relief was effective at reducing future risk in patients with moderate-to-severe asthma. However, improvements in mean FEV_1 and asthma symptom scores were not significantly different between the treatment groups.

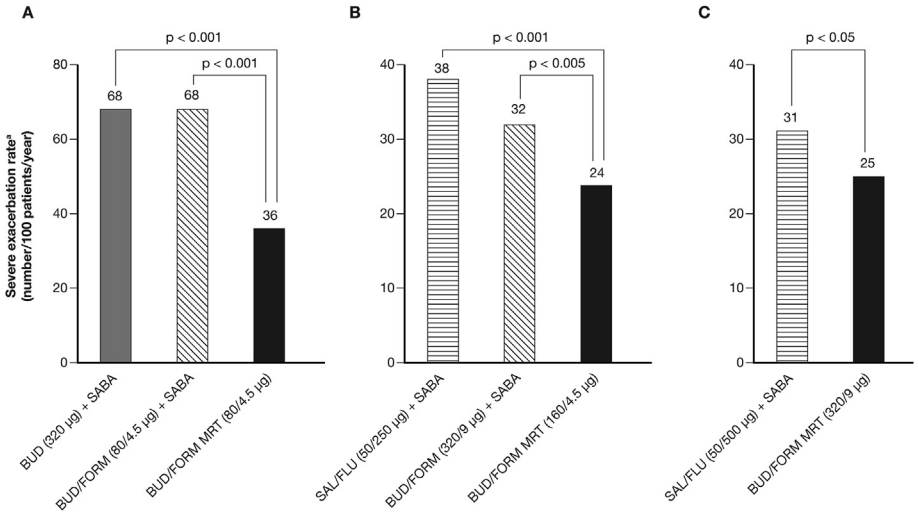

Fig. 4. Rate of severe asthma exacerbations with twice-daily treatment in STAY (A) [14], COMPASS (B) [16] and AHEAD (C) [17]. [a]Severe asthma exacerbations were defined as deterioration in asthma resulting in: hospitalisation/ER treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning PEF of 70% or less of baseline on two consecutive days in STAY (A); hospitalisation/ER treatment, or the need for OCS for ≥3 days (as judged by the investigator) in COMPASS (B); hospitalisation/ER treatment and/or OCS treatment for ≥3 days in AHEAD (C). BUD, budesonide; ER, emergency room; FLU, fluticasone; FORM, formoterol; ICS, inhaled corticosteroid; MRT, maintenance and reliever therapy; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β_2-agonist; SAL, salmeterol.

4.2. ICS/LABA maintenance and reliever therapy: real-world studies

In addition to the studies discussed above, the use of budesonide/formoterol as maintenance and reliever therapy has been assessed in over 23,000 patients as part of four real-world studies that included comparisons with salmeterol/fluticasone or conventional best practice and an evaluation of a range of doses [18,29–31]. Budesonide/formoterol maintenance and reliever therapy was shown to improve asthma control and reduce the frequency of exacerbations compared with either salmeterol/fluticasone or conventional best practice [18,29]. Patients treated with budesonide/formoterol for maintenance and relief received a reduced overall mean daily dose of ICS compared with conventional best practice [29], and oral corticosteroid use was also lower than with salmeterol/fluticasone plus SABA or conventional best practice [18,29]. Interestingly, for patients treated with twice-daily budesonide/formoterol maintenance and reliever therapy at doses of 80/4.5 µg, 160/4.5 µg or 320/9 µg, reliever use was low irrespective of the dose received [31].

4.3. ICS/LABA maintenance and reliever therapy: airway inflammation and remodelling

As the use of ICS/LABA for both maintenance and relief may lead to a reduction in the dose of ICS required to maintain stable disease [34], concerns have previously been raised that this approach may reduce the frequency of exacerbations without controlling airway inflammation and remodelling [11,35]. In a 12-month, parallel-group, randomised study, patients were treated with budesonide/formoterol maintenance and reliever therapy (160/4.5 µg bd; delivered dose) or both budesonide/formoterol (320/9 µg bd) and budesonide (320 µg bd) plus SABA in order to determine if the lower maintenance dose of budesonide used in the maintenance and reliever therapy approach had an effect on airway eosinophils and remodelling [11]. Patients receiving budesonide/formoterol for maintenance and relief had significantly higher numbers of sputum and bronchial biopsy eosinophils than those in the comparator arm. However, these changes were relatively small and were not clinically meaningful, despite the very high dose of budesonide used in the comparator arm. Indeed, these variances were not associated with differences in exacerbation rate, lung function or changes in the fraction of exhaled nitric oxide. In addition, budesonide/formoterol maintenance and reliever therapy reduced airway remodelling as effectively as the high dose of budesonide/formoterol plus SABA, as indicated by the lack of between-group differences in reduction of reticular basement membrane thickness over 12 months.

5. Conclusions

In the pivotal FACET study, a lower dose of budesonide/formoterol improved current asthma control compared with a higher dose of budesonide alone, although the lower dose of budesonide/formoterol was associated with a smaller reduction in the exacerbation risk compared with a higher dose of budesonide alone [3]. Similarly, the GOAL study showed that addition of salmeterol to fluticasone improved health status and exacerbation risk compared with fluticasone alone, although it is not known whether this approach is more beneficial than increasing the dose of fluticasone monotherapy [4]. The use of ICS/LABA maintenance and reliever therapy provides an alternative strategy to fixed-dose ICS/LABA maintenance therapy plus SABA, reducing the frequency of exacerbations and improving asthma control in patients with previously poorly controlled asthma and a history of exacerbations. While one clinical study has demonstrated that beclometasone/formoterol maintenance and reliever therapy is more effective at reducing asthma exacerbations than beclometasone/formoterol plus SABA [19], there is a large body of evidence to show that treatment with budesonide/formoterol maintenance and reliever therapy improves both current control and future risk compared with ICS/LABA plus SABA or a higher dose of budesonide alone [12–18,28–31].

Author contributions

All authors participated fully at every stage in the development of this review.

Disclosure of potential conflicts of interest

René Aalbers has received speaker fees and research funding from AstraZeneca, speaker fees from Chiesi, Mundipharma, Boehringer Ingelheim and Novartis, and advisory board fees from AstraZeneca, Mundipharma, and Novartis.

Claus Vogelmeier has given presentations at symposia and/or served on scientific advisory boards sponsored by Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, and Takeda.

Piotr Kuna has given presentations at symposia and/or served on scientific advisory boards sponsored by Adamed, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, MSD and Novartis.

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